1183-67 Alteration of L-Type Calcium Currents in Human Cardiopathy

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Background. There are controversies concerning calcium currents changes associated with different stages of cardiopathy (compensated hypertrophy or heart failure).
Methods. Human myocytes (n=160) were obtained from right atrial appendages during open-heart surgery in 40 patients (pts) with acute (groupA) or chronic (group B) cardiopathy. Group A included pts with recent (less than one month) mitral regurgitation (MR) linked to chordal tendinee rupture (3 pts, n=13); group B included pts with chronic MR (6 pts, n=21), aortic stenosis (5 pts, n=16), aortic regurgitation (6 pts, n=32), ischemic cardiopathy (20 pts, n=78). Calcium current ICaL was recorded from freshly dissociated myocytes with the whole-cell patch-clamp technique. Cell capacitance (picofarad: pf), ICaL peak amplitude (picoampere: pA), and ICaL density (pA/pF) were measured. Left ventricular (LV) dilatation and/or hypertrophy (echocardiography), LV ejection fraction (angiographic determination), NYHA functional class, age and therapy were taken into account. Results. In group A, ICaL peak amplitude was 490+/-60pA, ICaL density was 6.5 +/-0.8 pA/pF, and cell capacitance was 76+/-15 pF. In comparison, group B was characterized by highly significant reduction of both ICaL peak and density (220+/-15 pA and 1.7 +/-2 pA/pF; p<0.0001) and by a twofold increase of cell capacitance (142+/-55 pF; p<0.001). In group B, cell capacitance was markedly larger in advanced (LVEF<35%) ischemic cardiopathy (178+/-13 pF; p<0.01) whereas a dramatic decrease of peak current was associated with chronic MR (98+/-34 pA; p<0.001). LVEF and NYHA class were not predictive of ICaL peak amplitude. Calcium channel antagonists and/or B-blockers therapy had no significant effect on current whereas age > 70 years and LV dilatation were significantly related to reduced ICaL density (p<0.01).
Conclusion. There is a reduction of ICaL peak density associated with chronic cardiopathy in human. However, decrease in peak ICaL amplitude and/or increase in cell capacitance may have variable contribution in different diseases. Alteration of calcium currents in right atrial myocytes may reflect involvement of hemodynamic, neurohormonal or systemic factors.

1183-68 Pur β, a Single Stranded DNA Binding Protein Represses SRF Mediated Muscle Gene Expression: Implications in Impaired Cardiac Muscle Gene Expression During Heart Failure

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Background: Pur proteins play a role in cell growth and differentiation by modulating cell cycle progression, replication and transcription of certain genes including smooth muscle actin. We have previously identified a strong negative regulatory element (PNR) at +66 to +108 bp region of cardiac αMHC gene. PNR collaborated with positive regulatory factors α interacting within the -200 bp promoter region of this gene, encompassing SREs (serum response elements). We subsequently cloned one of the transcription factors binding to PNR as Purβ. This study examined the role of Purβ in SRF mediated activation of α-MHC gene promoter.
Methods: Transient transfection assays in primary cultures of cardiomyocytes analyzed the effect of SRF or Purβ, alone or in combination on α-MHC promoter activity using luciferase as reporter. Gel -shift assay analyzed DNA-protein interaction.
Results: Transfection of SRF cDNA activated α-MHC promoter/luciferase activity by 3 to 5 fold. Inclusion of Purβ expression vector reduced SRF mediated activation by 1 to 2-fold. Purβ alone caused 40% repression of basal activity of α-MHC gene promoter. Gel-shift assay using cardiac and Sol8 nuclear extracts and SRE of α-MHC demonstrated two DNA-nuclear protein complexes, upper complex (UC) and lower (LC) complex. Super shift assay using specific antibody against Purβ established LC as Purβ. The specificity of this interaction in cardiac nuclear extract was examined further by using SREs of various muscle genes and of c-fos gene. Muscle SREs produced UC and LC whereas c-fos SRE produced only UC. Purified GST- Purβ protein showed sequence specific interaction with three different SREs of muscle genes but none with c-fos SRE. Competitive binding was observed between in vitro synthesized SRF and GST- Purβ for muscle SRE. Western blot and Northern blot analysis showed 3-fold induction in Purβ expression in rat hearts subjected to pressure load with 70% decrease in α-MHC mRNA was observed.
Conclusion: Purβ through its interaction with SRE represses SRF mediated activation of α-MHC gene expression. Increased level of this protein in pressure load hypertrophy suggest its involvement in reducing the mRNA level of α-MHC.

1183-69 Chronic Monotherapy With Extended Release Metoprolol Succinate Attenuates mRNA Gene Expression of Brain and Atrial Natriuretic Peptides in Left Ventricular Myocardium of Dogs With Heart Failure

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Background: Plasma levels of brain (BNP) and atrial (ANP) natriuretic peptides are increased in heart failure (HF) and are predictive of poor outcome. Therapy with extended release metoprolol succinate (ER-MET) was shown to reduce mortality and morbidity in patients with HF. We previously showed that monotherapy with ER-MET increases LV ejection fraction and attenuates LV remodeling in dogs with chronic HF. In the this study, we examined the effects of ER-MET, a selective β_1-receptor antagonist, on mRNA gene expression of BNP and ANP in LV of dogs with microembolization-induced HF. **Methods:** Total RNA was isolated from LV tissue of 14 dogs with HF randomized to 3 months therapy with ER-MET (50 mg, once daily, n=7) or to no therapy at all (n=7) and from LV of 6 normal (NL) dogs. Using specific primers in reverse transcriptase-polymerase chain reaction, BNP and ANP were identified on agarose-ethidium gel; corresponding fluorescent bands were quantified in densitometric units and normalized to glyceraldehyde-3 phosphate dehydrogenase (GAPDH), a housekeeping gene. **Results:** The results are shown in the table. Expression of both BNP and ANP increased in untreated HF dogs compared to NL. Treatment with ER-MET reduced mRNA expression of both BNP and ANP when compared to untreated HF dogs. **Conclusions:** The findings indicate that in dogs with HF, monotherapy with ER-MET reduces mRNA expression of both BNP and ANP. These findings are consistent with the observed reduction in mortality and morbidity in patients with HF.

	NL	HF-Untreated	HF + ER-MET
BNP/GAPDH	0.54 ± 0.02	1.60 ± 0.10*	0.64 ± 0.07*^
ANP/GAPDH	0.48 ± 0.05	1.32 ± 0.03*	0.82 ± 0.03*^

*=P<0.05 vs. NL; ^=P<0.05 vs. HF-Untreated

POSTER SESSION

1184 Pharmologic Therapies

Tuesday, April 01, 2003, Noon-2:00 p.m.
McCormick Place, Hall A
Presentation Hour: 1:00 p.m.-2:00 p.m.

1184-70 Carvedilol Treatment Is as Well Tolerated as Angiotensin Converting Enzyme Inhibition in Patients With Chronic Heart Failure: Results of the CARMEN (Carvedilol ACE Inhibitor Remodeling Mild CHF EvaluatioN) Study

Michel Komajda, Hugo Madeira, Kristian Thygesen, Marco Bobbio, Wybren Jaarsma, Guenther Riegger, Jordi Soler-Soler, Lars Ryden, Per Hildebrandt, Beatrix Lutiger, Willem Remme, on behalf of the CARMEN investigators, Pitie Salpetriere Hospital, Paris, France, STICARES Cardiovascular Research Foundation, Rhoon, The Netherlands

Background: Although current treatment guidelines for chronic heart failure (CHF) recommend ACE-I and β-blockers, β-blockers are still grossly underused. Their historical contra-indication and the perception of a difficult up-titration might have added to the slow uptake of β-blockers despite their proven reduction of mortality and morbidity in CHF patients. The aims of the CARMEN study were to compare the effects on cardiac remodeling, safety and tolerability of the ACE-I Enalapril (E) against Carvedilol (C) a combined $\beta_1/\beta_2/\alpha_1$- blocker.
Methods: CARMEN is a parallel-group, 3-arm, double-dummy study conducted in 13 European countries. Patients were randomized to C&E, C or E treatment arms, uptitrated on C to 25mg (50mg in patients ≥ 85kg) bid target dose and/or E to 10mg bid target dose, and continued for 18 months. In the C&E arm, C was uptitrated first. Effects on left ventricular (LV) remodeling were assessed by echocardiography at baseline, months 6,12 and 18. Hospitalizations and deaths were adjudicated by a blinded endpoint committee.
Results: The safety population included 572 mild CHF patients (C&E = 191; C = 191; E = 190). Mean age was 62 years, with 81% male. 65% were treated with an ACE-I whereas only 6% received a β-blocker prior to study start. LV end systolic volume index was reduced in both C&E and C groups, but not in E. Similar percentages of patients were withdrawn 31%, 30% and 30%, experienced serious adverse events (AE) 28%, 29% and 34% and any AE 79% (497 AE), 77% (426 AE) and 75% (461 AE) in the C&E, C and E arm, respectively. The number of deaths was equal in all groups (N=14) with 6, 9 and 10 cardiovascular deaths in the C&E, C and E arm, respectively. All-cause and cardiovascular hospitalizations occurred in 26%, 27% and 32% and in 8%, 10% and 15% of patients in the C&E, C and E arms, respectively. Notably, there was no difference in AE during uptitration.
Conclusion: All three treatment arms showed a very similar safety profile. In contrast to common perception, there was no difference in tolerability between an ACE-I and C. This result is even more remarkable as the high prestudy use of ACE-I might have introduced a bias by selecting ACE-I tolerant patients, who were only switched from their former ACE-I to E.

1184-71 Predictors of β-blocker Utilization in Managed Care Patients With Heart Failure

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Background: Heart failure(HF) is an increasing cause of mortality and morbidity. Despite clinical trials and evidence-based guidelines that recommend β-blockers in patients with systolic dysfunction, utilization is low. The North Carolina Achieving Cardiac Excellence Project is designed to increase the utilization of angiotensin converting enzyme inhibitor(ACE-I) and β-blocker therapies in managed care patients(pts) with systolic HF. The purpose of this study is to determine the predictors of β-blocker prescription at baseline.
Methods: Data obtained from outpatient medical record abstraction were available for 1501 pts treated for HF in 2000. Pts on dialysis or with contraindications to β-blockers